

31 MAY 2005

DECLARATION

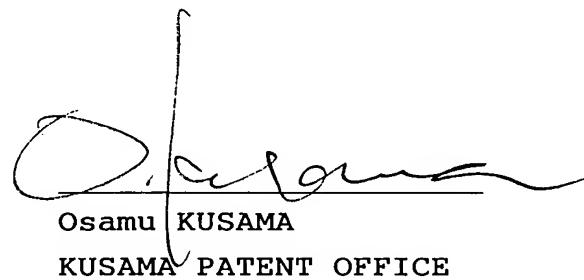
In the matter of an Application for Letters Patent by
TEIKOKU SEIYAKU CO., LTD. and FUSO PHARMACEUTICAL INDUSTRIES,
LTD.,

I, Osamu KUSAMA, Patent Attorney, whose full post office
address is 7th Floor, Iwata Bldg., 5-12, Iidabashi 4-chome,
Chiyoda-ku, Tokyo 102-0072, Japan, do solemnly and sincerely
declare as follows:

1. I am well acquainted with Japanese and English language.
2. The following is the true translation into English language
of the PCT application No. JP2002-233470 by TEIKOKU SEIYAKU
CO., LTD. and FUSO PHARMACEUTICAL INDUSTRIES, LTD. with the
Receiving Office / The Japanese Patent Office on August 9, 2002
in respect of an Application for Letters Patent.

And I make this solemn declaration conscientiously
believing the same to be true.

Declared at Tokyo, Japan
This 22nd day of February, 2005.



Osamu KUSAMA
KUSAMA PATENT OFFICE

(Translation)

JAPAN PATENT OFFICE

5 This is to certify that the annexed is a true copy of the following application as filed with this office.

Date of Application: August 9, 2002

10 Application Number: Patent Application No. 2002-233470
[ST.10/C]: [JP2002-233470]

Applicant(s): TEIKOKU SEIYAKU CO., LTD.
FUSO PHARMACEUTICAL INDUSTRIES, LTD.

15

July 29, 2003

20 Yasuo IMAI
Commissioner, Japan Patent Office

25

[Name of Document] Application for Patent

[Reference No.] TK335

[Addresses] To Commissioner of the Patent Office

[Inventor]

5 [Address] 2460-2, Kamosho, Shido-cho, Okawa-gun, Kagawa
[Name] SUGAWARA, Takaya

[Inventor]

[Address] 402-1, Tahishimomachi, Takamatsu-shi, Kagawa
[Name] SHIRAI, Sadanobu

10 [Inventor]

[Address] Room 506, 1608-1, Sanbonmatsu, Ohchi-cho, Ohkawa-
gun, Kagawa
[Name] YAMAJI, Masahiro

[Applicant for the Patent]

15 [Identification No.] 000215958
[Name] TEIKOKU SEIYAKU CO.,LTD.

[Representative]

[Identification No.] 100083301

[Patent Attorney]

20 [Name] Osamu Kusama

[Charge]

[Account Number] 053958

[Total Amount] ¥21,000

[List of the Documents]

25 [Item] Specification 1
[Item] Figure 1
[Item] Abstract 1

[General Power of Attorney No.] 9703083

JP2002-233470

[Proof]

Requested

【Name of the Document】 DESCRIPTION

【Name of the Invention】 NORETHISTERONE-CONTAINING EXTERNAL PATCH

【Claims】

【Claim 1】 An external norethisterone-patch comprising a
5 backing and a pressure-sensitive adhesive layer, wherein the
pressure-sensitive adhesive layer is made of an acrylic pressure-
sensitive adhesive containing, as an essential ingredient, contains
1 to 30% by weight of isopropyl myristate as a distribution
coefficient control agent and 0.5 to 10% by weight of norethisterone
10 and/or its derivative as an active ingredient.

【Claim 2】 The external patch according to claim 1, wherein
the backing is a laminate structure comprising a polyethylene
terephthalate film having a thickness of 0.1 to 10 μm and a flexible
polymer film, a non-woven fabric, or a woven fabric having a
15 thickness of 1 to 200 μm .

【Detailed Description of the Invention】

【0001】

【Technical Field】

The present invention relates to an external patch containing
20 norethisterone (a progestational hormone) and/or its derivatives
useful for prevention or treatment of diseases such as menopausal
syndrome (e.g., headaches, hot flushes, sweating, etc.) which often
occurs in climacteric or menopausal women, osteoporosis, Alzheimer's
disease, arteriosclerosis, and hyperlipemia.

25 【0002】

【Background Art】

In recent years, hormone replacement therapy is becoming
established as an important method for preventing or treating

diseases such as menopausal syndrome (e.g., headaches, hot flushes, sweating, etc.) which often occurs in climacteric or menopausal women, osteoporosis, Alzheimer's disease, arteriosclerosis, and hyperlipemia or for improving the QOL of middle-aged and older women.

5 【0003】

In order to prevent, treat, or improve such diseases, a hormone drug is orally administered or injected in most cases. However, it is known that in the case where a progestational hormone norethisterone is orally administered, the female hormone is 10 absorbed from the alimentary canal and is then rapidly metabolized in the liver. Likewise, it is known that such a estadiol administered by injection is also rapidly metabolized in the liver. Therefore, in either case, the rate of utilization of the drug is significantly low.

15 【0004】

Further, there is a possibility that not only impaired liver function but also side effects such as gallbladder disorder and uterine cancer are produced due to a high metabolic rate in the liver. Therefore, it is necessary to keep the drug concentration 20 (i.e., a hormone administered) in the body at a minimum. For this reason, methods for administering a female hormone without allowing the female hormone to pass through the alimentary canal or the liver are being investigated. Among such methods, attention is particularly being given to transdermal absorption preparations from 25 the viewpoint of excellent sustainability in drug release and handleability, and some preparations have already been studied.

【0005】

For example, Japanese Patent Publication No. Hei 6-51623

discloses a reservoir-type transdermal absorption preparation in which estradiol and norethisterone acetate are dissolved in a gel made of hydroxypropyl cellulose and ethanol. This reservoir-type transdermal absorption preparation controls the release of estradiol 5 and norethisterone acetate by the use of an ethylene-vinyl acetate film. However, since the preparation contains a volatile ingredient, there is a fear that drug release characteristics may be changed. In addition, the preparation involves the risk of causing skin troubles such as rubor because ethanol contained therein is an irritant to 10 the skin.

【0006】

Further, International Publication No. WO 91/17752, Japanese Patent Laid-Open Publication No. Hei 5-148145, and Japanese Patent Laid-Open Publication No. 2000-119195 disclose patches manufactured 15 using rubber pressure-sensitive adhesives such as a styrene-isoprene-styrene block copolymer. However, since the patch is manufactured using natural rubber or synthetic rubber as a pressure-sensitive adhesive, they are not suitable for prolonged skin application from the viewpoint of the characteristics of natural 20 rubber or synthetic rubber.

【0007】

For example, Japanese Patent Laid-Open Publication No. Hei 4-342532 discloses a patch manufactured using an acrylic pressure-sensitive adhesive comprising 2-ethylhexyl acrylate and N-vinyl-2-pyrrolidone. However, since this preparation contains N-vinyl-2-pyrrolidone in a high concentration, norethisterone as a basis is 25 dissolved in the pressure-sensitive adhesive, thus resulting in poor releasability of norethisterone from the preparation. In addition,

this preparation has a problem in that it causes strong physical irritation to the skin due to its excessive adhesive strength. Therefore, the preparation cannot be used for prolonged and continuous administration.

5 **【0008】**

Moreover, in the case where an external preparation is administered in hormone replacement therapy, it is necessary to apply the external preparation for a long period of time to maintain an effective blood level of a drug. In order to apply the external preparation for a long period of time, it is necessary to improve the adhesive strength of a base material of the external preparation. In addition, it is particularly necessary to enhance the anchor effect of a pressure-sensitive adhesive on the irregularities of the skin surface in order to increase a holding power. The anchor effect of a pressure-sensitive adhesive on the irregularities of the skin surface can be enhanced by increasing the activity of a polymer compound as an adhesive base material. However, by doing so, there is a possibility that the cohesive strength of the polymer compound is lowered so that cohesion failure occurs, thus resulting in the remaining of the pressure-sensitive adhesive on the skin after peeling-off of the external preparation. Therefore, it is necessary to control the anchor effect of the pressure-sensitive adhesive and the cohesive strength of the pressure-sensitive adhesive to allow the external preparation to be applied for a long period of time.

25 **【0009】**

In many articles, it has already become apparent that the flexibility of a backing of an external patch has a strong bearing on an increase of the transdermal drug absorption. Examples of a

backing having physical properties adequate for this purpose include low-density polymer films, non-woven fabrics, and woven fabrics. It is necessary for them to have a free volume sufficient to obtain flexibility. However, when the free volume of the backing is too 5 large, there is a problem in that drug releasability is lowered after the external patch is stored for a long period of time due to the adsorption of a drug to the backing layer, so that such an external patch cannot deliver satisfactory performance.

【0010】

10 In many articles, it has already become apparent that the flexibility of a backing of an external patch has a strong bearing on an increase of the transdermal drug absorption. Examples of a backing having physical properties adequate for this purpose include low-density polymer films, non-woven fabrics, and woven fabrics. It 15 is necessary for them to have a free volume sufficient to obtain flexibility. However, when the free volume of the backing is too large, there is a problem in that drug releasability is lowered after the external patch is stored for a long period of time due to the adsorption of a drug to the backing layer, so that such an 20 external patch cannot deliver satisfactory performance.

【0011】

【The problem to be solved in the Invention】

In view of the above fact, it is therefore an object of the present invention to provide an external patch containing a 25 norethisterone and/or its derivatives and satisfying the following points (1) to (4):

- (1) having improved drug releasability per unit area;
- (2) having a low degree of skin irritation;

(3) having an improved adhesive strength enough to withstand prolonged application while preventing cohesive failure from occurring when the external patch is peeled off after the completion of prolonged application; and

5 (4) having a flexible backing enabling the transdermal absorbability of a drug to be improved without the drug being adsorbed to the backing.

【0012】

【Means to solve the problem】

10 In order to achieve the above object, the present inventors have intensively investigated, and as a result, they have found, in the case where a female hormone to be contained in the external patch is a progestational hormone norethisterone and/or its derivative, that a distribution coefficient between the preparation and the skin is an important factor, that isopropyl myristate is effective in controlling the distribution coefficient of norethisterone contained in the acrylic pressure-sensitive adhesive, and that isopropyl myristate is preferably contained in the acrylic pressure-sensitive adhesive layer at an optimum ratio, thereby 15 reducing skin irritation. These findings have led to the completion 20 of the present invention.

【0013】

According to a first aspect of the present invention according to claim 1 based on the basic concept provided by the invention, 25 there is provided a norethisterone (progestational hormone)-containing external patch comprising a backing and a pressure-sensitive adhesive layer, wherein the pressure-sensitive adhesive layer is made of an acrylic pressure-sensitive adhesive containing 1

to 30% by weight of isopropyl myristate as a distribution coefficient control agent and 0.5 to 10% by weight of norethisterone and/or its derivative as an active ingredient.

【0014】

5 In the external norethisterone (progestational hormone)- containing patches according to claim 2 of the present invention, it is more preferred that the backing be a laminate structure according to claim 1 of the present invention comprising a polyethylene terephthalate film having a thickness of 0.1 to 20 μm and a flexible 10 polymer film, a non-woven fabric, or a woven fabric having a thickness of 1 to 200 μm .

【0015】

The present invention is characterized in that a distribution coefficient between the preparation and the skin is an important 15 factor, that isopropyl myristate is effective in controlling the distribution coefficient of norethisterone contained in the acrylic pressure-sensitive adhesive, and that isopropyl myristate is preferably contained in the acrylic pressure-sensitive adhesive layer at an optimum ratio, thereby reducing skin irritation.

20 【0016】

【BEST MODE FOR CARRYING OUT THE INVENTION】

As described above, the present invention is characterized in that a pressure-sensitive adhesive layer is made of an acrylic pressure-sensitive adhesive containing a 1 to 30% by weight of 25 isopropyl myristate, and further containing a norethisterone and/or its derivative as an active ingredient.

【0017】

The amount of an active ingredient norethisterone and/or its

derivative to be mixed is not particularly limited and varies depending on a pressure-sensitive adhesive component to be used, the amount of isopropyl myristate to be mixed, and the structure of a backing to be used (which will be described later), but is in the 5 range of 0.5 to 10% by weight, preferably in the range of 1 to 7% by weight, more preferably in the range of 3.0 to 5 % by weight. If the amount of norethisterone and/or its derivative to be mixed is less than 0.5% by weight, the level of norethisterone and/or its derivative in the blood does not become sufficient. On the other 10 hand, even if the amount of norethisterone and/or its derivative to be mixed exceeds 10% by weight, an increase in the mixing ratio thereof does not proportionately increase the level of norethisterone and/or its derivative in the blood. In addition, there is an undesired possibility that norethisterone and/or its 15 derivative is crystallized in the pressure-sensitive adhesive.

[0018]

As adhesive base materials used in manufacturing an external patch, natural rubber, synthetic rubber pressure-sensitive adhesives, acrylic pressure-sensitive adhesives, and silicon pressure-sensitive 20 adhesives are generally known. The present inventors have found that in the case where natural rubber or a synthetic rubber pressure-sensitive adhesive is used as an adhesive base material of an external patch, the releasability of a norethisterone and/or its derivative as an active ingredient contained in a pressure-sensitive 25 adhesive layer is lowered due to a strong interaction between the natural rubber or the synthetic rubber pressure-sensitive adhesive and the norethisterone and/or its derivative.

[0019]

In addition, since natural rubber and synthetic rubber pressure-sensitive adhesives are inherently hydrophobic, they are not resistant to sweat and water. Therefore, in hot and humid surroundings or during taking a bath or exercise, there is a 5 possibility that sweat or water enters between the pressure-sensitive adhesive layer and the skin, thus resulting in a reduction in the migration of a drug to the skin or separation of the external patch from the skin. From the fact, it can be said that such an external patch manufactured using natural rubber or a synthetic 10 rubber pressure-sensitive adhesive as an adhesive base material is not suitable for prolonged application that is one of the requirements of a preparation of the present invention.

【0020】

Further, in the case where a silicon pressure-sensitive 15 adhesive is used as an adhesive base material, final material composition becomes specific. Since this becomes a factor of an increase in cost, a silicon pressure-sensitive adhesive is not preferable. As a result of investigation, the present inventors have found that an acrylic pressure-sensitive adhesive is most preferable 20 as an adhesive base material for use in manufacturing the external patch of the present invention containing a norethisterone and/or its derivative as an active ingredient.

【0021】

Examples of a monomer constituting the acrylic pressure- 25 sensitive adhesive include acrylic acid, vinyl acetate, and acrylic esters such as ethyl acrylate and 2-ethylhexyl acrylate.

【0022】

The amount of each of the monomer components to be mixed is

appropriately determined according to, for example, desired physical properties of an acrylic pressure-sensitive adhesive to be obtained, but 2-ethylhexyl acrylate is preferably contained in an amount of 5 to 50 % by weight, acrylic acid is preferably contained in an amount 5 of 1 to 10 % by weight, ethyl acrylate is preferably contained in an amount of 5 to 50% by weight, and vinyl acetate is preferably contained in an amount of 5 to 50% by weight.

【0023】

Norethisterone and/or its derivative has a high degree of 10 solubility in the acrylic pressure-sensitive adhesive, which leads to poor releasability of a drug from the pressure-sensitive adhesive. However, by allowing isopropyl myristate to be contained in the adhesive base material, it becomes possible to control the distribution of norethisterone to the adhesive base material, 15 thereby improving the releasability of the drug.

【0024】

The amount of isopropyl myristate to be mixed is in the range of 1 to 30% by weight, preferably in the range of 3 to 20% by weight, more preferably in the range of 5 to 10% by weight. If the amount of 20 isopropyl myristate to be mixed is less than 1% by weight, the above effect cannot be obtained. On the other hand, if the amount of isopropyl myristate to be mixed exceeds 30% by weight, it becomes difficult to maintain the cohesive strength of the pressure-sensitive adhesive even when an excessive amount of crosslinking 25 agent is mixed, thereby, for example, causing a problem in that the pressure-sensitive adhesive remains on the skin surface after the external patch is peeled off.

【0025】

In the meantime, it has been already apparent that the flexibility of the backing of an external patch strongly contribute to the improvement of the transdermal absorbability of an active ingredient contained in a pressure-sensitive adhesive layer.

5 Examples of a backing having physical properties adequate for such a purpose include low-density polymer films, non-woven fabrics, and woven fabrics. In the case where they are used singly as a backing, it is necessary for them to have a sufficient volume to obtain flexibility. Therefore, an external patch manufactured in such a 10 manner involves a problem in that drug releasability is lowered after the external patch is stored for a long period of time due to the occurrence of adsorption of a drug to the backing, so that the external patch may not be satisfactory. In the case of the external patch of the present invention containing a female hormone as an 15 active ingredient, it is necessary to avoid lowering of drug releasability as far as possible.

[0026]

In view of such a problem, the present inventors have made investigation of a backing suitable for an external patch containing 20 a norethisterone and/or its derivative as an active ingredient. As a result, it has been confirmed that the use of a laminate structure comprising a drug non-adsorptive layer having a very thin and dense structure and a flexible film capable of following the 25 irregularities on the skin or body movements as a backing makes it possible to prevent the adsorption of the active ingredient to the backing, thereby improving the transdermal absorbability of a drug.

[0027]

Fig. 1 shows the structure of such a backing. As shown in Fig.

1, a backing A to be used for the external patch of the present invention is a laminate structure comprising a flexible film 1 and a drug non-adsorptive layer 2 having a thin and dense structure. The external patch of the present invention has a structure in which a 5 pressure-sensitive adhesive layer 3 containing an active ingredient is laminated on the drug non-adsorptive layer 2 and a release liner 4 is laminated on the pressure-sensitive adhesive layer 3.

【0028】

As described above, the backing A to be used for the external 10 patch of the present invention is characterized in that the drug non-adsorptive layer 2 having a thin and dense structure is provided on the pressure-sensitive adhesive layer to prevent the adsorption of an active ingredient to the backing and the flexible film 1 is provided to allow the external patch to follow the irregularities on 15 the skin or body movements.

【0029】

The drug non-adsorptive layer is not limited to any specific one as long as it has a dense structure, can be formed into a thin film, and does not interact with the components of the pressure- 20 sensitive adhesive layer, such as an active ingredient. Examples of such a drug non-adsorptive layer include metal films, evaporated metals, and high-density polymer films (polyethylene terephthalate film). Among them, a polyethylene terephthalate film is preferable from the viewpoint of versatility and manufacturing costs. The 25 thickness of the drug non-adsorptive layer e.g., a polyethylene terephthalate film is preferably in the range of about 0.1 to 20 μm . If the thickness of the polyethylene terephthalate film exceeds 20 μm , the external patch cannot follow the irregularities on the skin

or body movements due to the stiffness of the polyethylene terephthalate film, and therefore the transdermal absorbability of an active ingredient contained in the pressure-sensitive adhesive layer is lowered.

5 【0030】

On the other hand, the flexible film to be laminated on the drug non-adsorptive layer is not limited to any specific one as long as it can follow the irregularities on the skin or body movements. Examples of such a flexible film include woven fabrics, non-woven fabrics, and polymer films made of polyethylene, polypropylene, polyurea, polyurethane, polyester, polyvinyl alcohol, polyvinyl chloride, or polymeric elastomers. The thickness of the film is in the range of about 1 to 200 μm , preferably in the range of about 2 to 100 μm , more preferably in the range of about 5 to 50 μm .

15 【0031】

If the thickness of the flexible film layer is less than 1 μm , it is difficult to apply a preparation to the skin because the preparation is bent or warped when the release liner is removed due to the lack of elasticity. On the other hand, if the thickness of the flexible film layer exceeds 200 μm , it becomes difficult for a preparation to follow the irregularities on the skin surface or body movements so that the transdermal absorbability of an active ingredient is lowered.

【0032】

25 The external patch according to the present invention can be manufactured, for example, in such a manner as described below. 39 % by weight of 2-ethylhexyl acrylate, 1% by weight of acrylic acid, 40 % by weight of ethyl acrylate, and 20% by weight of vinyl acetate

are mixed, and are then subjected to polymerization for 24 hours at 60°C under reduced pressure in ethyl acetate by the use of benzoyl peroxide as a polymerization initiator to obtain an ethyl acetate solution of an acrylic pressure-sensitive adhesive. A female hormone 5 estradiol and/or its derivative or norethisterone and/or its derivative as an active ingredient and desired components are added to the acrylic pressure-sensitive adhesive solution and then stirred. The thus obtained mixture is applied on a release liner and dried, and then a backing is laminated thereon. The thus resultant product 10 is cut into a desired size to obtain an external patch.

【0033】

In the external patch of the present invention manufactured in such a manner, since a norethisterone and/or its derivative as an active ingredient contained in the pressure-sensitive adhesive layer 15 is well dissolved in the pressure-sensitive adhesive layer, the active ingredient is not adsorbed to the backing. In addition, the external patch per se can follow the irregularities on the skin surface or body movements. Therefore, the external patch can provide an excellent transdermal absorbability of an active ingredient 20 contained in the pressure-sensitive adhesive layer and can withstand prolonged application. Such an external patch is useful for prevention or treatment of diseases such as menopausal syndrome (e.g., headaches, hot flushes, sweating, etc.) which often occurs in 25 climacteric or menopausal women, osteoporosis, Alzheimer's disease, arteriosclerosis, and hyperlipemia.

【0034】

Hereinbelow, the present invention will be described in more detail with reference to Examples. Incidentally, the word "part" in

the following Examples and Comparative Examples means "part by weight."

【0035】

Examples 1 to 3 :

5 According to the manufacturing method described above and a formula shown in Table 1, norethisterone acetate-containing external patches of the present invention were obtained. Each of the norethisterone acetate-containing external patches of Examples 1 to 10 3 was manufactured by laminating a pressure-sensitive adhesive layer on a polyethylene terephthalate film constituting a backing (a laminate structure) having a predetermined thickness and cutting the thus obtained product into a desired size.

【0036】

【Table 1】

Constituent (part)	Examples		
	1	2	3
Norethisterone acetate	5.00	5.00	5.00
Isopropyl myristate	5.00	10.00	20.00
Acrylic pressure-sensitive adhesive	89.80	84.80	74.80
Isocyanate-based crosslinking agent	0.20	0.20	0.20
Backing	Thickness (μm)		
Polyethylene terephthalate film	3	3	3
Low-density polyethylene film	50	50	50

15 **【0037】**

Comparative Examples 1 to 6 :

According to the manufacturing method described above and a formula shown in Table 2, norethisterone acetate-containing external patches of Comparative Examples 1 to 6 were obtained. Each of the 20 norethisterone acetate-containing external patches of Comparative Examples 1 to 6 was manufactured by laminating a pressure-sensitive adhesive layer on a polyethylene terephthalate film constituting a

backing having a predetermined thickness and cutting the thus obtained product into a desired size.

Note that Comparative Example 4 used a low-density polyethylene film having a thickness of 50 μm as a backing (a monolayer structure), Comparative Example 5 used a polyvinyl chloride film having a thickness of 50 μm as a backing (a monolayer structure), and Comparative Example 6 used a polyurethane film having a thickness of 50 μm as a backing (a monolayer structure). Each of the norethisterone acetate-containing external patches of Comparative Examples was manufactured by laminating a pressure-sensitive adhesive layer on the backing and cutting the thus obtained product into a desired size.

【0038】

【Table 2】

Constituent (part)	Comparative Examples					
	1	2	3	4	5	6
Norethisterone acetate	5.00	5.0	5.0	5.0	5.0	5.0
Isopropyl myristate	-	10.00	10.00	10.00	10.00	10.00
Acrylic pressure-sensitive adhesive	94.8	84.80	84.80	84.80	84.80	84.80
Isocyanate-based crosslinking agent	0.2	0.2	0.2	0.2	0.2	0.2
Backing	Thickness (μm)					
Polyethylene terephthalate film	3	30	50	-	-	-
Low-density polyethylene film	50	50	50	50	-	-
Polyvinyl chloride film	-	-	-	-	50	-
Polyurethane film	-	-	-	-	-	50

【0039】

Test Example 1: In Vitro Permeation Test in Rat

The abdominal region of a rat was shaved, and then the

abdominal skin was extracted. The extracted skin was placed in a Franz cell, and the inside of the cell was filled with 10 mL of phosphate buffered saline (a receptor solution). In a water jacket, a hot water having a temperature of 37°C was circulated. Each of the 5 external patches of Examples 1, 2, and 3 and Comparative Example 1 was stamped into a circular shape (1.77 cm²), and was then applied to the extracted skin of the rat. The receptor solution was sampled with the lapse of time to measure the amount of norethisterone that passed through the skin and eluted into the receptor solution 10 according to a liquid chromatography method.

[0040]

The result is shown in Fig. 2. As is apparent from Fig. 2, in the case of the external patch of Comparative Example 1 containing no isopropyl myristate as a distribution coefficient control agent 15 in the adhesive base material, the permeation amount of norethisterone was extremely small as compared to the cases of Examples 1, 2, and 3. From these results, it can be concluded that isopropyl myristate contained in the adhesive base material has the effect of promoting the absorption of norethisterone.

[0041]

Test Example 5: Measurement of Level of Norethisterone in Blood of Rats

Four rats were used as one test group. The back region of each of the rats was shaved, and then the external patches of 25 Example 1 and Comparative Examples 2 and 3 each having a size of 9 cm² were applied to the back regions shaved of the rats, respectively. The blood of each of the rats was sampled with the lapse of time to measure the level of norethisterone in the blood according to a gas

chromatography method. The measurement results are shown in Fig. 3.

[0042]

As is apparent from the Figure, in the case of the external patch of Example 1 manufactured using, as a backing, a laminate structure comprising a polyethylene terephthalate film having a thickness of 3 μm and a low-density polyethylene film having a thickness of 50 μm , the level of norethisterone in the blood remained at an obviously higher level by virtue of the flexibility of the backing as compared to the cases of the external patch of Comparative Example 2 manufactured using, as a backing, a laminate structure comprising a polyethylene terephthalate film having a thickness of 30 μm and a low-density polyethylene film having a thickness of 50 μm and the external patch of Comparative Example 3 manufactured using, as a backing, a laminate structure comprising a polyethylene terephthalate film having a thickness of 50 μm and a low-density polyethylene film having a thickness of 50 μm .

[0043]

Test Example 4: Active Ingredient Release Test after Storage (Part 2)

The external patches of Example 1 and Comparative Examples 4, 5, and 6 were stored for 6 months at 40°C, and were then subjected to a release test according to a method shown in Fig. 4 to determine the adsorbability of norethisterone to the backing. The adsorbability of norethisterone to the backing was evaluated by comparing the releasability of norethisterone between the external patch after 6-month storage and the external patch in the initial state after manufacturing. The results are shown in Figs. 5, 6, 7, and 8.

In each of the cases of the external patch manufactured using a low-density polyethylene film as a backing (Comparative Example 4, Fig. 6), the external patch manufactured using a polyvinyl chloride film as a backing (Comparative Example 5, Fig. 7), and the external 5 patch manufactured using a polyurethane film as a backing (Comparative Example 6, Fig. 8), it can be concluded the releasability of norethisterone as an active ingredient was impaired due to the occurrence of adsorption of norethisterone to the backing.

[0044]

10 On the other hand, in the case of the external patch of Example 1 manufactured using a laminate structure comprising a polyethylene terephthalate film and a low-density polyethylene film as a backing (Fig. 4), the releasability of norethisterone was not impaired even after the external patch was stored for 6 months at 15 40°C. From the result, it was confirmed that the adsorption of norethisterone to the backing did not occur.

[0045]

[Industrial applicability]

20 In the pressure-sensitive adhesive layer containing norethisterone and/or its derivative, isopropyl myristate is further contained in the pressure-sensitive adhesive layer at a specific ratio. The external patch of the present invention makes it possible to highly dissolve a drug in the pressure-sensitive adhesive and stabilize the drug. In addition, it becomes also possible to improve 25 the transdermal absorbability of a medical ingredient and release the drug stably for a long period of time without adsorption of the drug to the backing.

[Brief Description of Drawings]

【Figure 1】 Fig. 1 is a cross-sectional view of an external patch of the present invention.

【Figure 2】 Fig. 2 is a graph, which shows the result of Test Example 1 in which the level of norethisterone in the blood was 5 measured in rats.

【Figure 3】 Fig. 3 is a graph, which shows the result of Test Example 2 in which the level of norethisterone in the blood was measured in rats.

【Figure 4】 Fig. 4 is a schematic view of an apparatus for use in 10 carrying out a release test in Test Example 3.

【Figure 5】 Fig. 5 is a graph, which shows the result of Test Example 3 carried out using an external patch of Example 1.

【Figure 6】 Fig. 6 is a graph, which shows the result of Test Example 3 carried out using an external patch of Example 4.

【Figure 7】 Fig. 7 is a graph, which shows the result of Test Example 3 carried out using an external patch of Comparative Example 5.

【Figure 8】 Fig. 8 is a graph, which shows the result of Test Example 3 carried out using an external patch of Comparative Example 20 6.

【DESCRIPTION OF THE SYMBOLS IN THE DRAWINGS】

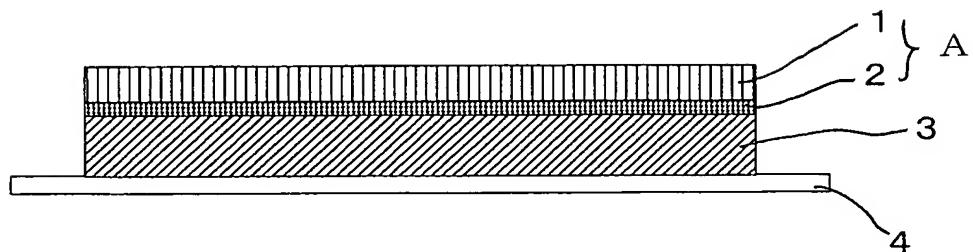
- A: backing
- 1: flexible film
- 2: drug non-adsorptive layer
- 25 3: pressure-sensitive adhesive layer
- 4: release liner
- 5: patch
- 6: water

7: glass plate

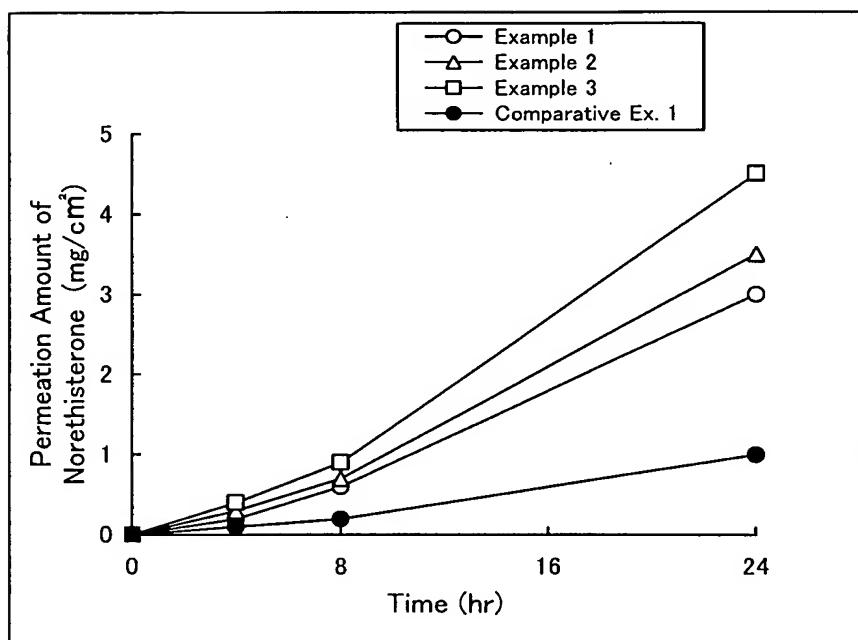
8: stirrer

[Name of the Document] Figure

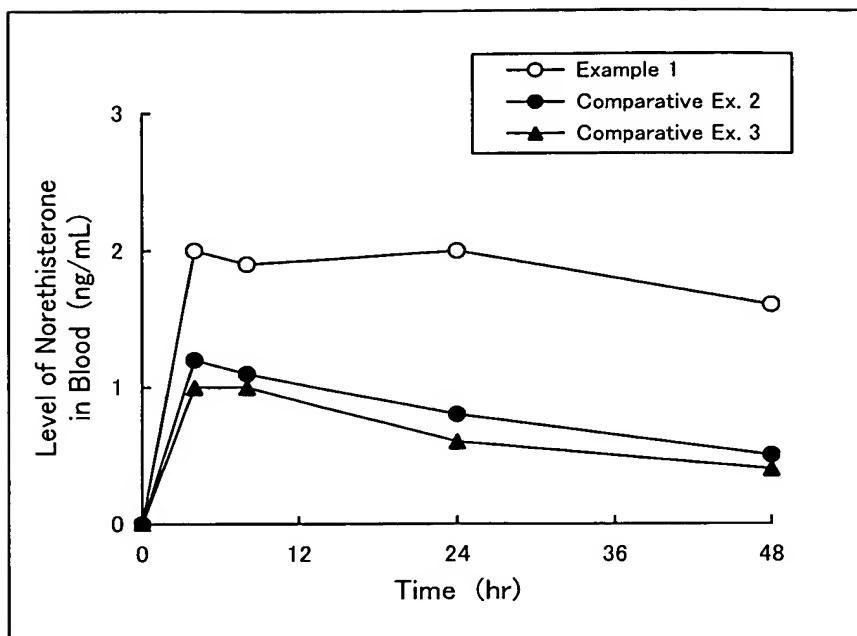
[Fig.1]



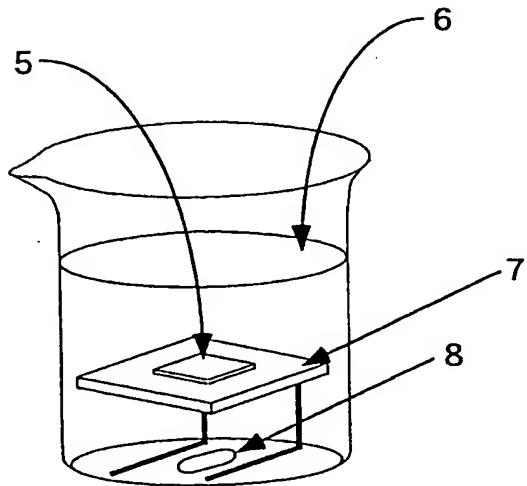
[Fig.2]



[Fig.3]

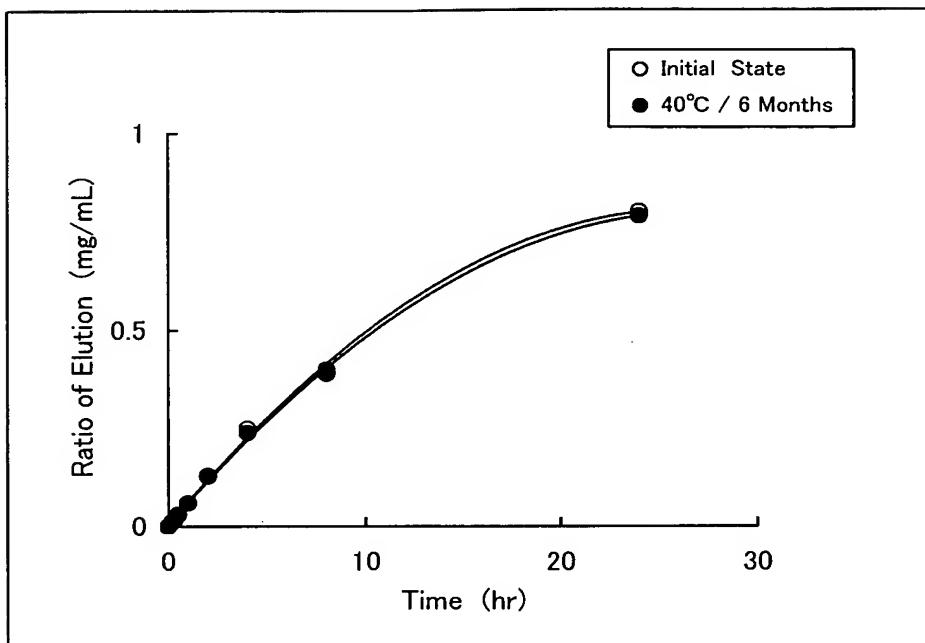


[Fig.4]

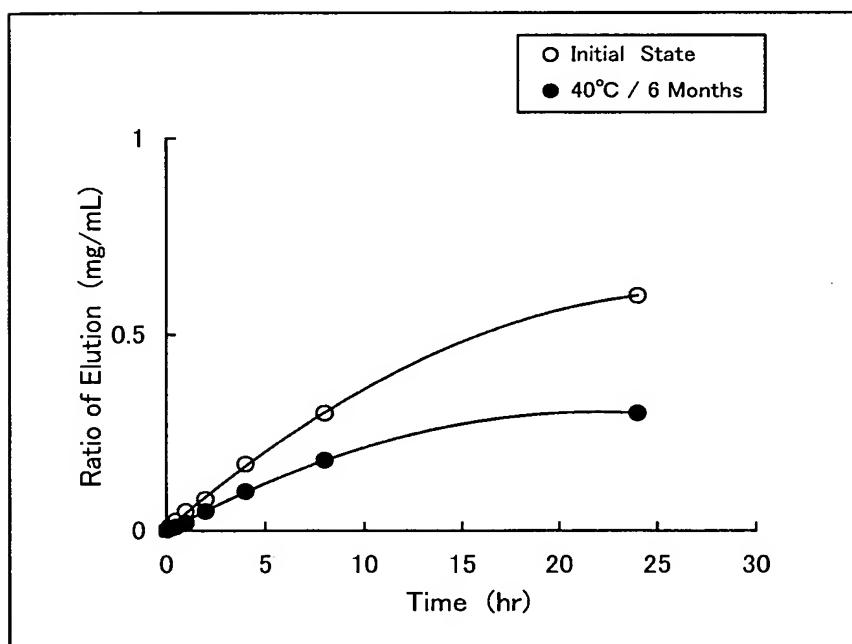


5

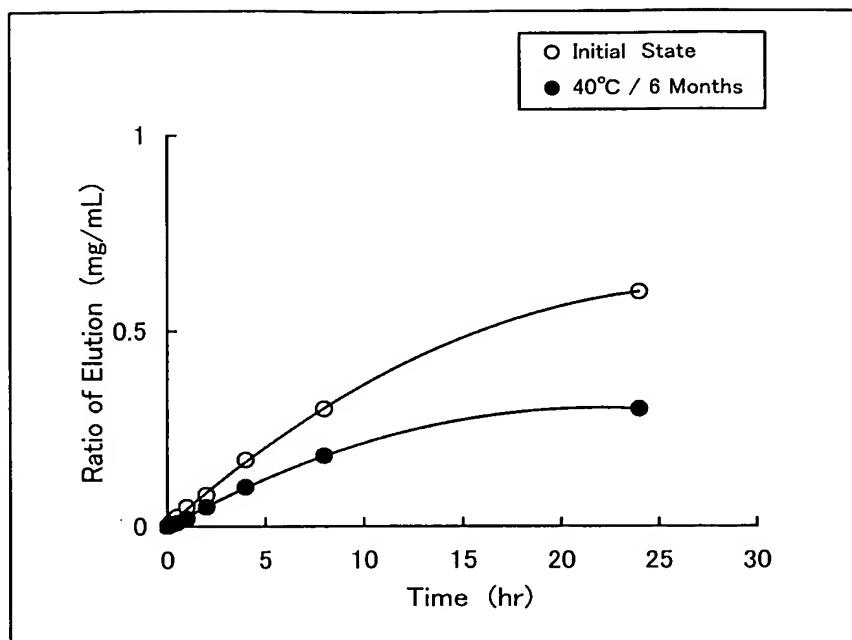
[Fig.5]



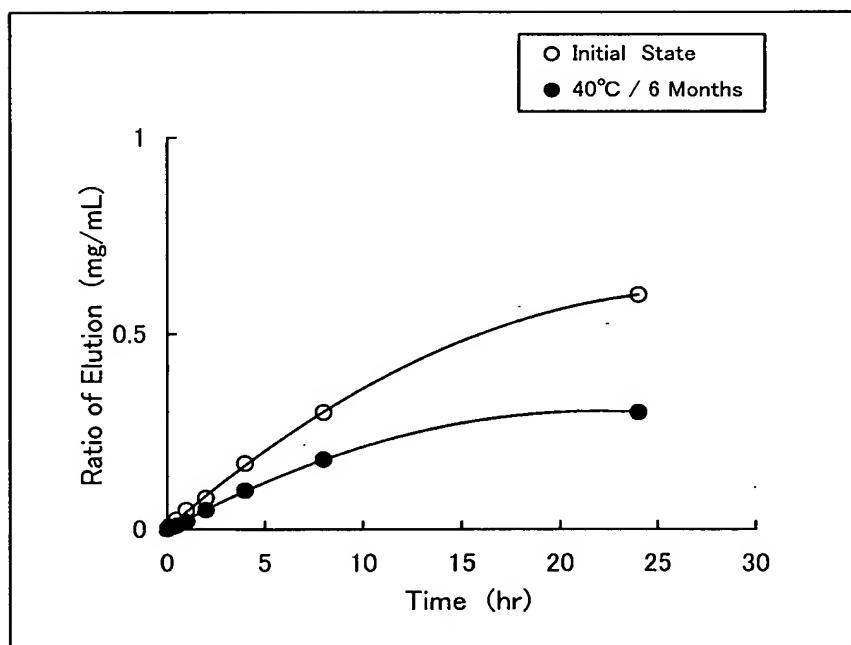
[Fig.6]



[Fig. 7]



[Fig. 8]



[Name of the Document] ABSTRACT

[Abstract]

[Purpose] Provided herein is a norethisterone-containing patch wherein an active ingredient is highly soluble in a pressure-sensitive adhesive layer and the active ingredient is not adsorbed to a backing, and the patch per se can follow the irregularities on the skin surface or body movements.

[Means to solve the problem] An external patch comprising a backing and a pressure-sensitive adhesive layer, wherein the pressure-sensitive adhesive layer is made of an acrylic pressure-sensitive adhesive containing contains 1 to 30% by weight of isopropyl myristate as a distribution coefficient control agent and 0.5 to 10% by weight of norethisterone and/or its derivative as an active ingredient.

15 **[Selected Figure]** Fig.3

Approval and Addition Information

Patent Application # Patent Application # 2002-233470
Reference Number 50201193596
5 Name of Document Application for Patent
Responsible Officer No.6 Upper Class 0095
Date Heisei 14 August 12

<Approval Information and Addition Information >

10 [Date of Submission] Heisei 14 August 9

[Name of Document] Request for change of person

[Reference No.] TK335

[Addresses] To Commissioner of the Patent Office

[Identification of the Case]

5 [Application No.] Patent Application No. 2002-233470

[Assignee]

[Equity] 001/002

[Identification No.] 00238201

[Name] Fuso Pharmaceutical Industries, Ltd.

10 [Representative] TODA, Mikio

[Agent for Assignee]

[Identification No.] 100083301

[Patent Attorney]

[Name] Osamu Kusama

15 [Charge]

[Account Number] 053958

[Total Amount] ¥4,200

[Proof] Requested

Approval and Addition Information

31 MAY 2005

Patent Application # Patent Application # 2002-233470
Reference Number 50300823515
5 Name of Document Request for change of person
Responsible Officer KANESAKI, Sadao 6996
Date Heisei 15 June 24

<Approval Information and Addition Information >

10 [Date of Submission] Heisei 15 May 19
[Assignee]
[Identification No.] 000238201
[Address] 7-10, Doshomachi 1-chome, Chuo-ku,
Osaka-shi, Osaka
15 [Name] Fuso Pharmaceutical Industries, Ltd.
[Agent for Assignee] Applicant
[Identification No.] 100083301
[Address] 7F, Iwata Bldg., 5-12, Iidabashi 4-
chome, Chiyoda-ku, Tokyo
20 [Name] Osamu Kusama

Information on the applicant's personal history

Identification Number	[000215958]
5 1. Date of Change	August 8, 1990
[Reason for Change]	New Registration
Address	567, Sanbonmatsu, Ohuchi-cho, Ohkawa-gun, Kagawa
Name	TEIKOKU SEIYAKU CO.,LTD.
10	
2. Date of Change	April 2, 2003
[Reason for Change]	Change of address
Address	567, Sanbonmatsu, Higashikagawa-shi, Kagawa
15 Name	TEIKOKU SEIYAKU CO.,LTD.

Information on the applicant's personal history

Identification Number [000238201]

5 1. Date of Change August 8, 1990

[Reason for Change] New Registration

Address 7-10, Doshomachi 1-chome, Chuo-ku,
Osaka-shi, Osaka

Name Fuso Pharmaceutical Industries, Ltd.

10

JP2002-233470